AWARD NUMBER: W81XWH-14-1-0373

TITLE: Tranexamic Acid Mechanisms and Pharmacokinetics in Traumatic Injury

PRINCIPAL INVESTIGATOR: Philip C. Spinella, MD

CONTRACTING ORGANIZATION: Washington University
St. Louis, MO 63110

REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2015	Annual	22 Sep 2014 - 21 Sep 2015

4. TITLE AND SUBTITLE
Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0373

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Philip Spinella, M.D.
Grant V. Bochicchio, MD, MPH

E-Mail: spinella_p@kids.wustl.edu ; bochicchiog@wudosis.wustl.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Washington University
660 S. Euclid Avenue
Campus Box 8116
St. Louis, MO 63110-1010

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our major accomplishments during the first year of the study include attainment of FDA IND approval, successful execution and completion of the community consultation process, development and validation of the laboratory methods for the trial, development of case report forms and database, attainment of Barnes Jewish Hospital Emergency Medicine Research Committee approval and WU IRB approval of the study pending minor contingencies. In addition, we have worked with Investigational Drug Pharmacy to plan for randomization, study drug preparation and dispensing procedures, and un-blinding procedures (in case of a safety concern). We have developed a process for our Vascular Surgery colleagues to schedule the lower extremity duplexes being performed for this study. Finally, we have established a DSMB and DSMB charter.

15. SUBJECT TERMS

Trauma, hemorrhage, transfusion, fibrinolysis, immune suppression, pharmacokinetics, outcomes, adverse events.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified		19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Title: Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury

(TAMPITI Trial)

Annual Report YR 1

Award Number: W81XWH-14-1-0373
Log Number: 13335005

Philip C. Spinella, MD
Grant V. Bochicchio, MD, MPH

Table of Contents

Page No.

1. INTRODUCTION:

This single center randomized controlled trial in adult patients with severe traumatic injury will determine if the use of tranexamic acid within 2 hours of injury is associated with less immune suppression compared to placebo. Tranexamic acid doses of 4g and 2g will be analyzed. In addition the pharmacokinetics of tranexamic acid will be established in addition to outcome and safety measures. We will also develop a biorepository of plasma samples for future analysis of coagulation and endothelial injury parameters.

2. KEYWORDS:

Trauma, hemorrhage, transfusion, fibrinolysis, immune suppression, pharmacokinetics, outcomes, adverse events.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Task 1: Obtain FDA IND and Community Consent for trial. (Timeframe: 1-6 months).

FDA IND approval was received 20-FEB-2015 (letter received 19-MAY-2015)

- Community Consultation Activities took place between 28-MAR-2015 and 18-MAY-2015 and the results of the activities were reported to the WU IRB and were reviewed by a full board on 23-SEP-2015. The WU IRB voted to approve the trial under the EFIC contingent upon minor revisions to the protocol and public disclosure plan and this notification was received on 02-OCT-2015.
    - We have made the requested revisions and have resubmitted to the WU IRB for their review and approval (resubmitted 09-OCT-2015). We expect WU final IRB approval in the next week and will then submit all documents to the DoD HRPO for their review and approval.
    - WU IRB review and approval was also contingent on the Barnes Jewish Hospital Emergency Medicine Research Committee's approval which was granted on 09-APR-2015.
- Secretary of the Army Approval was granted on 11-SEP-2015.

Task 2: Conduct a multi-center, double-blinded, Randomized Controlled Trial (RCT) of 150 patients with three study groups; TXA 2 gram IV bolus, TXA 4 gram IV bolus, and placebo. (Timeframe: months 7-32).

We estimate initiating the trial by 01- DEC-2015 as patient recruitment cannot begin until Public Disclosure activities have concluded and have been deemed sufficient and approved by the WU IRB.
We expect the clinical trial to be completed 01-JUL-2017.

What was accomplished under these goals?

Our major accomplishments during the first year of the study include attainment of FDA IND approval, successful execution and completion of the community consultation process, development and validation of the laboratory methods for the trial, development of case report forms and database, attainment of Barnes Jewish Hospital Emergency Medicine Research Committee approval and WU IRB approval of the study pending minor contingencies. In addition, we have worked with Investigational Drug Pharmacy to plan for randomization, study drug preparation and dispensing procedures, and un-blinding procedures (in case of a safety

concern). We have developed a process for our Vascular Surgery colleagues to schedule the lower extremity duplexes being performed for this study. Finally, we have established a DSMB and DSMB charter.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

After several months of community consultation activities, our research team has been able to reach out to the community via formal and informal events. We have exhausted efforts to obtain permission and/or access for formal and informal presentations. Our many attempts to reach out to our most at risk demographic (men aged 40 and African American and Caucasian races) have been challenging due to a lack of interest expressed by the leaders of organizations attended by them. Many community leaders were uncomfortable with presentations to their organizations about a study involving “trauma”, “bleeding”, etc. and suggested we use other avenues to reach the community (i.e. social media, signage, radio, the news, etc.). They conveyed that people would not be interested in spending their time without compensation or benefit to them for something they didn’t feel involved them. We attempted to educate all disinterested parties that trauma can happen to anyone and that these community consultation activities are to provide the community with information and a chance to “opt out”. Despite such challenges, we believe that we have met the requirements necessary for the community consultation phase of the EFIC. We are interested in directing efforts toward public disclosure activities once IRB approval has been received.

We received input from over 175 community members and have provided information to countless more individuals through social media, the internet, and informal communications taking place.

We plan to provide further information to the community regarding the investigation, risk and benefits, and information pertaining to the exception from informed consent for emergency research during the public disclosure phase of this study. We plan to do this on a on a much broader level utilizing local, and regional broadcasting, newspapers, town hall meetings, as well as posters and signage.

In addition, our website will remain active with links to surveys that community members can complete reflecting their understanding and opinions of the study as well as their demographic data. Our website will also continue to house information request forms as well as Opt Out request forms. Research team members will continue to be prompt in answering questions posed about the study as well as fulfilling Opt Out bracelet requests. We feel that the public disclosure phase that takes place before the study begins will be a positive extension to our community consultation efforts. We feel that the activities planned to take place during this phase will assist in reaching the demographic groups that we were challenged with due to our difficulty in securing informal and/or formal presentation opportunities that involve these groups. Our research team will continue to share the survey results for those completed online as well as document how often questions are posed and what the questions are centered around. Opt Out bracelet request fulfillment will also continue to be documented and shared with the IRB.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period we will obtain full WU IRB approval and DoD HRPO approval to begin recruiting patients into this clinical trial. We expect this to occur within the next month. The database for the trial will be complete by 01- NOV- 2015. We will begin training the research team in the trial methodology by 01-NOV- 2015 and plan to start enrolling patients shortly after this date. During the next reporting period we plan to enroll 10 patients per month. We will also prepare data for the DSMB scheduled meetings during the next reporting period.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  There have been formal (power point presentation at a variety of organized community meetings in addition to a presentation to the Barnes Jewish Hospital Emergency Medicine Research Committee) and informal presentations made to the community as part of our community consultation efforts.

  Journal publications.

  Nothing to Report

  Books or other non-periodical, one-time publications.

  Nothing to Report

  Other publications, conference papers, and presentations.

  Nothing to Report

- **Website(s) or other Internet site(s)**
  www.tampiti.wustl.edu
  - Our website disseminates the results of our recent community consultation activities and provides detailed information regarding the study (Investigators, design, sponsor, the problem, purpose, etc). The website also provides links to "opt out forms", "request information forms", contact information for the study team, links to our Facebook and Twitter pages, feedback forms, our community power point presentation, and the NIH video explaining emergency research and the EFIC, in addition to relevant references supporting the purpose of this study.

- **Technologies or techniques**

  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report

- **Other Products**

  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Philip C. Spinella, MD
Project Role:	PI
Research Identifier	ORCID ID: 0000-0003-1721-0541
Nearest person month worked	1

Contribution to Project:	Dr. Spinella has led the protocol and methods development for this trial in addition to the FDA IND submission. He assisted with several community consultation activities, conferred with the WU HRPO leadership to plan and execute this trial and has assisted with the WU IRB protocol submission and assembly of the DSMB/DSMP. He met with key stakeholders regarding this project (including the Emergency Medicine Leadership, HRPO leadership, etc.) and continues to assist with finalizing study execution logistics.
Funding Support:	During the reporting period, Dr. Spinella has had funding support from NIH/NHLBI (UO1HL072268, U01HL116383), CDI-EI-2015-499 and DoD.

Name:	Grant V. Bochicchio, MD
Project Role:	PD/PI
Research Identifier:	ORCID ID: 0000-0002-8313-1449
Nearest person month worked	1
Contribution to Project:	Dr. Bochicchio has assisted with the protocol and methods development, FDA IND submission, and WU IRB submission. He has participated in and has led several community consultation activities, conferred with the WU HRPO leadership to plan and execute this trial and has assisted with the assembly of the DSMB and DSMB. He met with key stakeholders regarding this project (including the Emergency Medicine Leadership, HRPO leadership, Trauma Surgery Faculty, etc.) and continues to assist with finalizing study execution logistics.
Funding Support:	During the reporting period, Dr. Bochicchio had funding support from Cook Biotech and NIH (5R44HL08629305, 5R34HL10936902).

Name:	Kelly Bochicchio, RN, MS
Project Role:	Clinical Research Specialist
Research Identifier	unknown
Nearest person month worked	3
Contribution to Project:	Ms. Bochicchio has functioned as the overall project manager for this trial. She has prepared all regulatory documents for submission, review, and approval to the WU IRB and DoD HRPO. She assisted with the FDA IND submission and organized and led the Community Consultation Activities. She has developed the Public Disclosure Plan activities that are forthcoming. She has assisted with the development of the Case Report Form, Randomization Plan, and Investigational Pharmacy dispensing procedures, created a process for duplexes to be performed according to study schedule and is responsible for the overall research team management.
Funding Support:	During the reporting period, Ms. Bochicchio had funding support from NIH (5R44HL08629305) and the Department of Defense (W81XWH1210550).

Name:	Anja Fuchs
Project Role:	Co-Investigator
Research Identifier	ORCID ID: 0000-0002-0186-4308
Nearest person month worked	1
Contribution to Project:	Dr. Fuchs has developed and validated laboratory techniques associated with the cytokine and PK/PD procedures being performed for this trial.
Funding Support:	During the reporting period, Dr. Fuchs had funding support from NIH (1R25NS09098501), The Foundation for Barnes-Jewish Hospital, and the American College of Surgeons.

Name:	Avril Adelman
Project Role:	Biostatistician
Research Identifier	unknown
Nearest person month worked	4
Contribution to Project:	Ms. Adelman has been developing case report forms and the database for this trial. In addition, she has assisted with deciding the randomization plan and reports to be presented to the DSMB.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS:

None

9. APPENDICES:

- TAMPITI Trial Community Consultation Evaluation (please see attached)
- SF 298

TAMPITI Trial Community Consultation Evaluation

MEETING:
Date: _____ Time: _____
Location: _____

	Strongly Agree (4)	***Agree (3)***	***Disagree (2)***	***Strongly Disagree (1)***
1. Has the TAMPITI Trial been explained to you so that you understand the risks and possible benefits?	□	□	□	□
2. I understand that if I am admitted to Barnes Jewish Hospital with a severe traumatic injury during the study period and the study team cannot reach a family member soon enough, I may be included in the study without consent.	□	□	□	□
3. Would you agree to participate in this study?	□	□	□	□
4. Would you agree to consent a family member into this study?	□	□	□	□
5. Are you supportive of this study being done in your community?	□	□	□	□
6. I understand how to obtain an **"OPT OUT TAMPITI"** Study bracelet and must wear it at all times if I do NOT wish to participate in this study	□	□	□	□

So that we can better understand who attended the meeting and use additional methods to reach subgroups that may not be represented, please complete the additional questions about you below:

8. Age (Circle One): **< 18** **18-25** **26-35** **36-45** **46-55** **over 55**

9. Gender (Circle One**):** **Male** **Female**

10. Ethnicity (Circle One): **Hispanic or Latino** **Non-Hispanic or Non-Latino**

11. Race: □ **White or Caucasian** □ **Native Hawaiian or Other Pacific Islander**
□ **Black or African American** □ **American Indian or Alaska Native**
□ **Asian** □ **Other:_____**